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09/506,078	02/16/2000	Manuel Campos	PC10202A	5616

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EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 05/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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APPLICATION NO./ CONTROL NO.09/506078	FILING DATE 2/16/2000	FIRST NAMED INVENTOR / Campos et al. PATENT IN REEXAMINATION	ATTORNEY DOCKET NO. 3153.00205

EXAMINER
Shanon Foley

ART UNIT	PAPER
1648	5134

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

Please find a copy of the Office action mailed August 27, 2003 and a copy of the amendment filed December 1, 2003.

Non final rejection after RCE - mailed 8/27/3

DETAILED ACTION

In paper no. 19, applicant amended claims 1, 3 and 11. Claims 1-17 are under consideration.

Request for Continued Examination

The request filed on 6/22/03 for a Request for Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/506078 is acceptable and a RCE has been established. An action on the RCE follows.

Specification

The specification is objected to for failing to adhere to the requirements of the sequence rules. Applicant must append SEQ ID Nos. to all mentions of specific sequences comprising four or more amino acids and ten or more nucleic acids in the specification. A specific example within the specification that does not comply with the sequence rules is found on page 2, lines 3 and 5. Applicant is required to append a SEQ ID NO. to any sequence within in the specification applicable to the rule. See 37 CFR § 1.821 (a)-(d) and MPEP § 2422.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1 and 3 have been amended to state that the second proteinaceous portion "synergistically affects the first proteinaceous portion by enhancing inhibition activity of the peptide that is analogous to said first proteinaceous portion". Applicant has not pointed to a section in the specification that supports this phrase and the examiner is unable to locate support. Applicant is requested to identify support for the amended phrase in the disclosure or cancel the new matter. This rejection affects all dependent claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. (US 5,684,145) and Zhu et al. (Vaccine. 1996; 14 (1): 61-69).

The claims are drawn to a conjugated protein producing a dual immune response in a vertebrate that comprises a first proteinaceous portion that is GnRH, the activity of this peptide is to be inhibited within the vertebrate. The second portion of this peptide is the immunogenic glycoprotein D (gD) from BHV-1. These proteins are encoded by a polynucleotide in a vector that is expressed in a transformed cell. A dual-function vaccine that comprises the fusion protein or the vector inhibits the activity of endogenous GnRH, which includes inhibiting the sexual

characteristics in a cow, and protects against BHV-1. The second proteinaceous portion synergistically affects the first proteinaceous of the conjugate.

Van Der Zee et al. teach a recombinant DNA molecule that codes for a hybrid protein comprising GnRH that is conjugated to *E. coli* fimbrial-filiments in a vaccine that elicits an immune response against GnRH. This recombinant DNA molecule is expressed in a host cell. See the abstract, example 1 in columns 14-16, claims 1-8. In example 3, adult rats that were given the plasmid containing the hybrid protein showed serum antibody binding and a disruption and suppression of estrous cycles, see Example 3, columns 16 and 17. Bulls that were immunized with the plasmid had a reduction of scrotal growth compared to control animals, see example 4 in column 18. The teachings of Van Der Zee et al. do not teach BHV-1 gD.

Zhu et al. teach inducing mucosal and systemic immunity against BHV-1 with glycoprotein D, see the abstract, figures 2 and 3, "Induction of mucosal and systemic immunity...", "Protection from BHV-1 challenge" on page 65 and the discussion section.

One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the *E. coli* P-fimbrial subunit portion of the hybrid protein of Van Der Zee et al. with the strongly immunogenic BHV-1 gD of Zhu et al. to evoke an immune response against GnRH and protect against BHV-1. One of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because the teachings of Van Der Zee et al. indicate that all that is needed to induce an immune response against GnRH is a strong immunogenic carrier (see columns 2-5 of Van der Zee et al.), which is what gD from BHV-1 is, see the previous citations of Zhu et al. as well as the full paragraph of the second column on page 61. Further, it is conventional practice in the vaccine arts to incorporate highly

antigenic glycoproteins into a vaccine; therefore, one of ordinary skill in the art would view the incorporation of gD into the hybrid protein taught by Van Der Zee as an obvious substitution over the *E. coli* fimbrial-filiments. Therefore, it is maintained that the instant invention would have been pima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence to evidence to the contrary.

Although neither Van der Zee et al. nor Zhu et al. teach that BHV-1 gD synergistically affects GnRH by enhancing inhibition activity of the peptide, Van der Zee et al. specifically teach that GnRH requires a strong immunogenic carrier to elicit an immune response, see the previous citations. Therefore, the *E. coli* P-fimbrial subunit portion of the hybrid protein of Van der Zee et al. is required to enhance the immune response against GnRH. The synergistic effect of the *E. coli* P-fimbrial subunit portion on GnRH is an inherent property of the strong immunogenic fusion carrier of Van der Zee et al. Since BHV-1 gD is also known as a strong immunogen that protects cows against BHV-1, fusion of the BHV-1 gD of Zhu et al. with GnRH of Van der Zee et al. would have the same inherent property as the *E. coli* P-fimbrial subunit portion of Van der Zee et al.

Applicant asserts that a fact-based explanation is required to explain why one of ordinary skill in the art would have been motivated to substitute the *E. coli* P-fimbrial subunit portion of Van der Zee et al. with the BHV-1 gD protein (taught by Zhu et al.) to evoke an immune response against GnRH and protect against BHV-1 infection.

In response, motivation for combining the proteins as a conjugate is found in the references themselves. Van der Zee et al. teach that immunization of GnRH is an effective contraceptive and is used to treat sexual hyperactivity, see column 1, lines 64-67 and columns 16

and 17. Van der Zee et al. specifically reduce the amount of scrotal growth in bulls by inducing an immune response against GnRH, see example 4 in column 18. Van der Zee et al. do not teach BHV-1 gD.

However, Zhu et al. teach BHV-1 gD protects cows against herpesvirus infection, see the previous citations.

One of ordinary skill in the art at the time the invention was made would have been motivated to exchange the *E. coli* P-fimbrial subunit portion of Van der Zee et al. with BHV-1 gD of Zhu et al. to simultaneously administer a contraceptive to cows, taught by Van der Zee et al. and protect cows against BHV-1, taught by Zhu et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for substituting the *E. coli* P-fimbrial subunit portion of Van der Zee et al. with the BHV-1 gD protein of Zhu et al. because Van der Zee et al. teach that GnRH requires a strong immunogen to invoke an immune response and Zhu et al. teach that BHV-1 gD is a strong immunogen.

Applicant further asserts that there must be a reasonable expectation of success for achieving and maintaining the dual function of the hybrid protein. Applicant states fusing proteins of different sources can affect the structural conformation and the functionality of the immunogenic sites and destroy the function of one or both of the fused proteins. Applicant has submitted a declaration by Mohamad A. Morsey as well as teachings by Bosch et al. and Agterberg et al., which questions the predictability regarding the function of fused proteins.

Applicant's arguments, declaration and a careful review of the references have been fully considered, but are found unpersuasive. First, the PhoE of *E. coli* K-12 protein discussed by the references does not have any structural or functional similarity to either GnRH or BHV-1 gD.

Second, both references discuss the effects of small inserts at different sites within PhoE of *E. coli* K-12 (emphasis added). The instant construct is drawn to a recombinantly conjugated protein comprising a first proteinaceous portion and a second proteinaceous portion. The instant conjugate does not comprise portions of the first or the second dispersed within one or the other protein. Therefore, the construct of Bosch et al. or Agterberg et al. does not bear any resemblance to the instant construct.

Further, it is maintained that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing a functional conjugated protein comprising the GnRH of Van der Zee et al. and the BHV-1 gD protein of Zhu et al. that protects cows against BHV-1 and functions as a bovine contraceptive. This reasonable expectation of success for producing the instant protein fusion is also found in the prior art.

Van der Zee et al. teach fusing GnRH and maintaining structural and functional epitopes required to induce an immune response against the protein in a fusion construct, see column 15, line 54 to column 16, line 15 as well as the previous citations. With respect to BHV-1 gD, the ordinary artisan would know the structural and functional epitopes of the glycoprotein that must be maintained to induce the protective immunity observed by Zhu et al. *supra* because Zhu et al. (Vaccine. January 21, 1999; 17: 269-282) properly fuse BHV-1 gD to IL-6 and demonstrate that the chimeric protein possesses the biological activity of both proteins, see figures 1, 5, 6, sections 3.6, 3.7 and the discussion section. In the first column of the discussion section, Zhu et al. (Vaccine. January 21, 1999; 17: 269-282) teach that antigenic areas of BHV-1 gD require proper folding to maintain reactivity with monoclonal antibodies and references the teachings of Van Druden Littel-Van den Hurk et al. (Virology. 1985; 144: 216-227). Van Druden Littel-Van

den Hurk et al. characterize the functional epitopes of BHV-1 gD in 1985, see the entire document. Therefore, ordinary artisan would know which structural epitopes would be required to be maintained within gD to elicit the functional protection against BHV-1. In conclusion, one of ordinary skill in the art at the time the invention was made would have had a more than reasonable expectation of producing a conjugated protein comprising GnRH and BHV-1 gD because the prior art clearly teach how to separately fuse each protein to other proteins and maintain the structural and functional integrity of each protein. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley